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ORIGINAL ARTICLE

Positive correlations of liver enzymes with metabolic syndrome including insulin resistance in newly diagnosed type 2 diabetes mellitus

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Abstract It has long been proposed that elevation of liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT) may be associated with insulin resistance (IR). In the present study, we aimed to investigate the association of the above mentioned liver enzymes with IR by using hyperinsulinemic euglycemic clamp, as well as their relationship with individual component of metabolic syndrome (MetS) in 95 newly diagnosed type 2 diabetes (T2DM) Chinese patients. All the diagnosed patients did not use drugs for treatment of diabetes or dyslipidemia previously and were divided into IR and non-IR groups. The results showed that IR group had significantly higher ALT, AST, and GGT ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively) compared with non-IR group. According to the individual MetS component, ALT and AST were significantly increased in patients with high blood pressure compared with those without (both $P < 0.001$); ALT and GGT were increased in patients with high triglyceride ($P < 0.05$ and $P < 0.01$); AST was increased in patients with central obesity ($P < 0.05$). In correlation analysis, a significant association was found between the three liver enzymes and clamp insulin sensitivity index (all $P < 0.001$). In the linear regression analysis, ALT was the determinant of clamp ISI, independent of age, sex, BMI, and fasting and OGTT 2 h plasma glucose ($P < 0.0001$). In conclusion, liver enzymes, especially ALT, were significantly associated with IR according to direct clamp assessment, which were independent of the traditional risk factors in diabetic patients; and individual liver enzymes may have different relationship with individual component of MetS.

Keywords Liver enzymes · Hyperinsulinemic euglycemic clamp · Insulin resistance · Metabolic syndrome

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Introduction

Liver is the main organ of glucose metabolism, where glucose uptakes, storages, synthesis, and metabolism of glucose occur [1]. Increased Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) are the most common indicators of liver disease. Increasing evidences show that elevated liver enzymes are observed in patients with diabetes mellitus, which are mostly attributed to fatty infiltration of the liver.

Insulin resistance (IR) is a central feature in the pathogenesis of T2DM and metabolic syndrome (MetS), predicting the development of diabetes in prospective studies [2–4]. A number of studies have reported that liver enzyme markers are associated with IR according to indirect measures such as fasting insulin levels and the homeostasis

model assessment of insulin resistance (HOMA-IR). However, information about the association of these markers with insulin sensitivity according to direct measurements like hyperinsulinemic euglycemic clamp technique is limited. Although some studies have shown that liver enzymes were associated with MetS, independently of potential confounders [5–9], it is still unclear about their individual involvement with MetS, and which one can be most accurately to indicate the incidence of MetS. Furthermore, T2DM, especially at early stage, might be associated with IR, however, the extent of their association could be different among patients, and it is also unclear whether there is a close relationship between liver enzymes levels and IR in these patients. Taken together, the objective of the present study is to present the evidence on the associations of liver enzymes (ALT, AST, and GGT) with IR through hyperinsulinemic euglycemic clamp among participants with T2DM in Shanghai, China. Moreover, the association of liver enzymes with individual component of MetS was examined.

Results

Characteristics of the study participants

The clinical and biochemical characteristics for the 95 patients were shown in Table 1. All the patients were divided into two groups (IR and non-IR group) according to the clamp ISI values obtained from a small cohort of healthy volunteers using the same methods in our department previously. We defined IR as a clamp ISI value <0.08 mg/kg min per μIU/ml. Compared with the non-IR group, IR group had significantly worse BMI, waist circumference,

Table 1 Characteristics of the 95 type 2 diabetes patients grouped by different insulin resistance status

Baseline variable	IR status	
	IR	Non-IR
n	60	35
Male/female	28/32	23/12
Age (years)	51.4 ± 9.1	52.8 ± 8.2
BMI (kg/m^2)	27.5 ± 3.3	24.9 ± 2.7‡
WC (cm)	94.3 ± 11.1	89.1 ± 8.0*
WHR	0.93 ± 0.08	0.91 ± 0.04
FPG (μU/ml)	7.1 ± 0.9	7.0 ± 1.1
Post load 2 hPG (μU/ml)	13.5 ± 2.8	10.6 ± 2.4†
Fasting Insulin (pmol/l)	11.0 (6.7–18.0)	7.3 (5.4–10.8)†
Post load 2 h Insulin (pmol/l)	47.8 (26.6–91.0)	32.8 (20.0–50.2)†
Systolic blood pressure (mmHg)	127.8 ± 15.1	125.3 ± 15.2
Diastolic blood pressure (mmHg)	83.3 ± 8.3	81.1 ± 8.3
TC (mmol/l)	5.25 ± 0.99	5.27 ± 1.05
TG (mmol/l)	1.88 (1.36–2.70)	1.80 (1.13–2.94)
HDL (mmol/l)	1.16 ± 0.26	1.22 ± 0.29
LDL (mmol/l)	3.14 ± 0.71	3.26 ± 0.89
ALT (units/l)	32.0(21.3–48.0)	21.0 (17.0–30.0)†
AST (units/l)	29.0 (20.0–34.5)	21.0 (18.0–24.3)†
GGT (units/l)	36.0 (23.3–58.8)	25.0 (20.0–40.0)*
HOMA-IR (μIUmol/l^2)	3.76 (2.01–6.41)	2.13 (1.50–3.72)†
Clamp ISI (mg/kg min per μIU/ml)	0.05 ± 0.02	0.12 ± 0.04‡
Number of MetS components	4 ± 1	3 ± 1*
Alcohol categories[a]	50/8/2	28/3/4

Data are means ± SD, medians (interquartile ranges) for skewed variables, or proportions for categorical variables. Differences were assessed using ANOVA tests (for continuous variables) or nonparametric tests (for categorical variables)

IR insulin resistance, was defined as a clamp ISI value < 0.08 mg/kg min per μIU/ml; *MetS* metabolic syndrome. Number of MetS components: in the present study, the minimum number is 1 and the maximum is 5

[a] Alcohol categories: "never/not regularly" (drinking alcohol < 5 g/week) vs. "low to moderate" (5–299 g/week), vs. "high quantities of alcohol consumption" (≥300 g/week) and "ex-drinkers"

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ vs. IR group

Table 2 Comparison for the liver enzymes between individual components of MetS relative to those without that combination

Individual components of MetS	ALT	AST	GGT
High blood pressure			
No	21.0 (17.0–32.0)	21.0 (18.0–24.0)	26.0 (18.0–36.0)
Yes	29.0 (21.0–50.0)‡	29.0 (20.0–33.0)‡	39.0 (23.0–53.0)
Low HDL			
No	27.5 (18.0–38.0)	21.5 (19.0–30.5)	31.5 (20.8–50.8)
Yes	28.0 (18.0–42.0)	27.5 (19.0–32.0)	29.0 (23.0–48.5)
High triglyceride			
No	23.0 (17.0–32.0)	21.5 (17.8–29.0)	24.0 (16.5–31.5)
Yes	29.0 (21.0–48.0)*	26.0 (20.0–33.0)	39.0 (24.0–58.3)†
Central obesity			
No	27.0 (18.0–32.0)	23.5 (19.0–27.0)	33.5 (21.5–62.0)
Yes	28.5 (18.0–42.5)	26.0 (19.0–32.3)*	30.0 (21.0–48.0)

See Table 1 for units.
* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

post load 2 h glucose concentration, fasting, and post load 2 h insulin concentrations ($P < 0.001$, $P < 0.05$, $P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively). The average number of MetS components was higher in the IR group than in the non-IR group ($P < 0.05$). The IR group also had significantly higher ALT, AST, and GGT ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively). The alcohol consumption status was not significantly different among the two groups.

The comparisons in the levels of the three liver enzymes between the group with one individual MetS component and the group without that component were shown in Table 2. Since all the participants in the present study were T2DM with hyperglycemia, only four MetS components (high blood pressure, low HDL, high triglyceride, and central obesity) except hyperglycemia were analyzed. Both ALT and AST were significantly higher in patients with high blood pressure than those without (both $P < 0.001$). Both ALT and GGT were higher in patients with high triglyceride than those without ($P < 0.05$ and $P < 0.01$, respectively) and AST alone was higher in patients with central obesity than those without ($P < 0.05$). However, no difference was found in the three enzymes between groups with and without low HDL ($P > 0.05$).

Table 3 Spearman correlation analysis on the associations of the liver enzymes with metabolic and antheropometric variables in all participants or participants excluding ex-drinkers and heavy drinkers

Variable	All participants			Excluding ex-drinkers and heavy drinkers		
	ALT	AST	GGT	ALT	AST	GGT
Age	−0.03	0.13	−0.12	−0.04	0.12	−0.12
BMI	0.26*	0.22*	0.09	0.26*	0.21	0.11
WC	0.17	0.20*	0.08	0.15	0.16	0.08
WHR	0.16	0.15	0.14	0.16	0.13	0.04
TC	0.12	0.17	0.17	0.16	0.21*	0.23*
TG	0.1	0.14	0.41‡	0.14	0.16	0.43‡
HDL	−0.17	−0.13	−0.13	−0.18	−0.13	−0.12
LDL	0.07	0.02	0.14	0.12	0.08	0.22*
Fasting glucose	0.02	0.04	0.06	−0.01	0.01	0.01
Post load 2-h glucose	0.25*	0.15	0.25*	0.24*	0.14	0.24*
Fasting insulin	0.33†	0.23*	0.41‡	0.34†	0.21*	0.44‡
Systolic blood pressure	0.2	0.04*	0.04	0.19	0.22*	0.03
Diastolic blood pressure	0.27*	0.15*	0.14	0.25*	0.26*	0.13
Degree of drink	−0.01	−0.04	0.26	–	–	–
HOMA-IR	0.29†	0.19	0.38‡	0.29†	0.17	0.40‡
Clamp ISI	−0.44‡	−0.45‡	−0.35†	−0.43‡	−0.43‡	−0.37‡
Number of MetS components	0.28†	0.37‡	0.23*	0.31†	0.41‡	0.30†

See Table 1 for units. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

Univariate analysis

Further correlation analysis was performed in these patients (Table 3). Univariate correlation analyses showed that all three liver enzymes were positively correlated with fasting insulin concentration and negatively correlated with clamp ISI. Both ALT and GGT were also significantly correlated with OGTT 2 h PG concentration and HOMA-IR. Furthermore, ALT, AST, and GGT were all significantly correlated with the increasing of the number of MetS components. The same results were obtained after excluding ex-drinkers, those who had quitted drinking for at least 5 years, and heavy-drinkers.

Adjusted analysis

In multiple stepwise regression analyses with a model including age, sex, BMI, waist circumference, systolic and diastolic blood pressure, fasting and post load 2 h PG and insulin, triglycerides, total, HDL, and LDL cholesterol, and the three liver enzymes as independent variables, ALT ($P = 0.007$), BMI ($P < 0.001$), OGTT 2 h PG ($P = 0.055$) and LDL cholesterol ($P = 0.059$) appeared to be the independent determinants of clamp ISI (total $R^2 = 0.353$; $P < 0.0001$).

Discussion

In the present study, we examined the role of the three liver enzymes, as clinical risk factors, in insulin resistance and metabolic syndrome in newly diagnosed T2DM patients in China. Our findings demonstrated that liver enzymes, AST, GGT, and ALT in particular, were significantly associated with IR as indicated by clamp ISI, independent of the traditional risk factors in diabetic patients. Although the three liver enzymes were all associated with the MetS components, individual component may have association with different enzymes.

Increased serum liver enzymes are conventionally considered as markers of alcohol abuse or liver damage. Although it has been known that liver dysfunction associated with chronic hepatitis or liver cirrhosis would result in glucose intolerance, it is only in recent years limited studies report elevated liver enzyme markers are also independent predictors of diabetes risk [10–14]. One prospective study in Pima Indians, high serum ALT concentrations were related to incident diabetes [15]. In the Mexico City Diabetes Study on nonalcoholic fatty liver disease (NAFLD), the positive correlation of increased serum GGT, ALT, AST, ALP levels with the risk of MetS, and T2DM was reported [7]. In addition, in some Japanese studies, GGT may correlate with hyperinsulinemia or IR [16], furthermore it could be a risk factor for MetS and T2DM [17].

Moreover, experimental and epidemiologic studies have shown that diabetes is associated with obesity, NAFLD, dyslipidemia, hyperinsulinemia, and hypertension [2, 18–22]; however, IR is the crucial factor. Therefore, our study confirmed the statistical significant relationship of liver enzymes with insulin resistance measured with clamp ISI.

This result is in accordance with one prospective study for older men aged 60–79 in Britain [6]. However, in the present study, when the clamp ISI was used as the assessment of IR, the linear regression analysis showed only ALT was the determinant of clamp ISI, independent of other confounding factors in T2DM. To date, only very few studies have examined the relationship between liver enzymes and clamp ISI, which was considered the golden standard for the insulin resistance. Vozarova et al. [15] reported a significant association of ALT with clamp-derived whole body insulin sensitivity in Pima Indians, independent of other risk factors. Similarly, Hanley et al. [2] reported ALT was associated with IR independently of conventional and more detailed metabolic measures in a multiethnic cohort. In the latter of the two studies, the frequently sampled intravenous glucose tolerance test (FSIVGTT) was used as the direct measure of insulin sensitivity; and our findings extended their observations with clamp ISI data in the Chinese population.

We further examined the association of liver enzymes with individual MetS components. In all the components of MetS, except hyperglycemia, high blood pressure is associated with both elevated ALT and AST, high triglyceride with elevated ALT and GGT, while central obesity with AST. However, we did not find any association of low HDL with these enzymes. Although, the association of liver enzymes and the incidence of MetS has been reported previously [5–9], conclusions are not consistent. The argument was focused on which enzyme might be the most important one for indicating the incidence of MetS and on their association with individual component. However, we found that different enzyme might have comparable values for predicting different components; and among the three enzymes, ALT showed relatively higher association with MetS and strongly associated with particular individual MetS components.

We used two different insulin resistance measures in our study to confirm the independent association between liver enzymes and insulin resistance. However, the present study is limited by the lack of direct measure of insulin resistance using clamp ISI in IGT and NGT subjects, which might have made our present conclusion more comprehensive.

In summary, our finding suggests that liver enzymes, especially ALT, were significantly associated with IR in diabetic patients, and different liver enzymes may have different relationship with individual component of MetS.

Materials and methods

Patients

For inclusion in the present study, we recruited 95 T2DM patients who were referred to the department of endocrinology in Ruijin Hospital (Shanghai) between May 2005 and June 2007. All the patients were newly diagnosed T2DM without present or previous use of drugs for treatment of diabetes or dyslipidemia. The T2DM diagnosis was according to the 1999 World Health Organization criteria [23]. The patients whose fasting plasma glucose ≥8 mmol/l and/or post load plasma glucose concentration ≥17 mmol/l, or having the histories of acute diabetic complications including diabetic ketoacidosis or hyperosmolar hyperglycemic non-ketotic coma were excluded. With the concern of some diseases which might have influence on liver enzymes levels, patients with moderate or severe liver dysfunction, including serum alanine aminotransferase >120 IU/l and aspartate aminotransaminase >80 IU/l were excluded; and all patients enrolled were those without present or previous history of hepatitis infection, which was obtained from filled out questionnaires or current hepatitis virus examination in those whose liver enzymes levels were above normal ranges; moreover, other clinical manifestations such as white blood cell count were also performed and must be within normal range to exclude chronic or acute inflammations, which might have influence on liver enzymes.

All subjects were Chinese living in the Shanghai region, and given informed consent. The Institutional Review Board of the Ruijin Hospital approved the study protocol.

Data collection

We used a questionnaire to collect information on smoking habits, alcohol intake, and disease history. The questionnaire provided information on the use of alcohol versus abstinence, and the frequency of the consumption of various types of alcoholic beverages during the past month. In the study area, beer is sold in bottles of 750 ml, whereas yellow aperitif, rice aperitif, and hard liquor are traded in units of 0.5 kg. We estimated that one unit of beer, aperitif, and liquor on average contained 30, 90, and 200 g of ethanol, respectively. In the current analysis, from the type and quantity of the alcoholic beverages used, we computed alcohol consumption in grams per week to categorize participants in four items: "never/not regularly" (drinking alcohol <5 g/week), "low to moderate" (5–299 g/week), "high quantities of alcohol consumption" (≥300 g/week) and "ex-drinkers" [24]. The "ex-drinker" related to those who have stopped drinking for at least 5 years regardless of the amount of alcohol consumed.

Clinical and biochemical measurements

The same physician measured body height, body weight, and waist and hip circumferences. Body mass index was calculated as body weight in kilogram divided by body height squared in meters. The height and weight of each subject were recorded with the subject wearing light clothes but no shoes, and body mass index (BMI) (kg/m^2) was calculated. Blood pressure was measured at the right arm three times consecutively with 1-min interval after at least 5 min rest with the subject in a sitting position; the averages of the three values were used in this analysis.

Blood samples were collected after an overnight fast for the determination of plasma hepatic enzyme of ALT, AST and GGT; fasting and 2-h post-load plasma glucose (PG), and other parameters such as triglycerides, total, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol and blood white cell counting. The assay was done by the enzymatic method with an autoanalyzer (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA) in the hospital laboratory using commercial reagents. Plasma glucose was measured by the enzymatic hexokinase method. We measured serum insulin concentration by a radioimmunoassay (Sangon Company, Shanghai, China). Serum AST and ALT values of greater than 40 IU/l were defined as elevated AST and ALT, respectively, and serum GGT greater than 50 IU/l was defined as an elevated GGT, on the basis of reference values provided by manufacturers of the reagents.

Serum samples, urine samples, and DNA samples were collected, stored in freeze refrigerator at the −80°C temperature.

Hyperinsulinemic euglycemic clamp

All the patients underwent hyperinsulinemic euglycemic clamp test for the assessment of insulin sensitivity as described previously [25]. Briefly, the hyperinsulinemic euglycemic clamp study was performed 6–8 days following OGTT. A small polyethylene catheter was placed in an antecubital vein for blood sampling. The hand engaged for the blood sampling was kept in a heated box at 50–60°C. A second catheter was placed in a vein in the contralateral forearm for infusion of insulin and 20% dextrose solution. After a 30–45 min stabilization period, a 10-min priming insulin infusion was administered, followed by a constant infusion of 60 mU/m^2 surface area per min over 140 min. 20% glucose was infused at a variable rate beginning 4 min after initiation of the insulin infusion to maintain blood glucose concentrations at steady state 5.0–5.5 mmol/l. During the clamp, blood glucose levels were repeatedly measured at the intervals of 5 min with a glucose analyzer (Biosen 5130, Neckar Healthcare. Co. Ltd. Magdeburg,

Germany). Blood samples for insulin measurement were collected at 10 min intervals.

The clamp insulin sensitivity index (Clamp ISI, mg/kg min per μIU/ml) was defined as the ratio of glucose disposal rate (the amount of the glucose supplied to maintain blood glucose levels during the last 30 min of the clamp) to insulin concentration at the end of the clamp.

All the patients were divided into two groups (IR and non-IR group) according to the clamp ISI values obtained from a small cohort of healthy volunteers using the same methods in our department previously. Among these healthy volunteers (No. = 10, male/female: 6/4), their mean age were 52.3 ± 5.8 years, clamp ISI values were 0.20 ± 0.12 mg/kg min per μIU/ml. The cut point for IR was defined as values of the lower 10% in the healthy subjects which was 0.08 mg/kg min per μIU/ml.

We also used the formulas HOMA-IR to calculate the degree of IR by fasting plasma glucose (FPG) and fasting insulin (FINS): HOMA-IR = (FPG × FINS)/22.5.

Definitions

Type 2 diabetes was diagnosed according to the 1999 World Health Organization criteria (fasting plasma glucose level ≥ 7.0 mmol/l or 2 h OGTT plasma glucose level ≥ 11.1 mmol/l) [23]. A fasting glucose level less than 6.1 mmol/l and a 2 h OGTT plasma glucose level less than 7.8 mmol/l were defined as normoglycemia.

Metabolic syndrome was defined according to the updated 2005 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [26]. In details, the definition of metabolic syndrome requires the presence of any three or more of the following five criteria: (1) high blood pressure: blood pressure ≥130/85 mmHg or known treatment for hypertension; (2) hypertriglyceridemia; fasting plasma triglycerides ≥1.7 mmol/l; (3) low HDL: fasting HDL cholesterol <1.0 mmol/l in men, <1.3 mmol/l in women; (4) hyperglycemia: fasting glucose level of ≥6.1 mmol/l or known treatment for diabetes; (5) central obesity: waist circumference >90 cm in men, >80 cm in women.

Statistical analysis

We used SPSS version 13.0 (SPAA, Chicago, IL, USA) for database management and statistical analysis. Baseline means (±SD), medians (with interquartile range) were used. Comparisons between subjects in IR and non-IR groups were assessed by one way-ANOVA test. The relationship between liver enzymes and anthropometric and metabolic variables was examined by Spearman correlation coefficients. Multiple linear regression models were used to examine the relationships after adjusting for covariates and confounders. *P* value of less than 0.05 was considered statistically significant. Since liver injury is closely related to heavy drinking, we repeated the analyses described above excluding ex-drinkers and heavy drinkers.

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Conflict of interest statement None.

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